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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/598,982	06/21/2000	Mark Maffitt	34506.104	6761

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EXAMINER	
RAMIREZ, DELIA M	
ART UNIT	PAPER NUMBER
3652	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/598,982	MAFFITT ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/27/2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-61* is/are pending in the application.

4a) Of the above claim(s) *26-33,38-40 and 43-61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,19-25,34-37,41 and 42* is/are rejected.

7)☒ Claim(s) *17 and 18* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 June 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

Claims 1-61 are pending.

Applicants elected with traverse Group I, claims 1-25, 34-37, 41-45, 54-58 drawn to DNA constructs, host cells encoding and expression of recombinant human tryptases, in Paper No. 8, filed on 2/21/2002. Arguments in regard to this restriction requirement were discussed at length by the Examiner in Paper No. 9, mailed on 5/22/2002.

In response to a supplemental restriction submitted in Paper No. 9, mailed on 5/22/2002, Applicants have further elected with traverse the polynucleotide of SEQ ID NO: 20 as the polynucleotide to which claims 1-25, 34-37, 41-45, 54-58 are partially drawn, in Paper No. 11, filed on 11/27/2002.

Applicant's traverse is on the ground(s) that if the members of a Markush group are sufficiently small in number or closely related, so that the entire claim can be examined without serious burden, the Examiner must examine the entire claim set on the merits. It is Applicant's opinion that all the polynucleotides recited in the application encode human tryptases and they are thus very closely related. Applicants assert that all the differences between the proteins encoded by the recited DNA molecules are point mutations at one or more amino acid positions 44, 91 and 194. Therefore, Applicants argue that examination of all the recited DNA molecules does not place an undue burden upon the Office. Also, Applicants have indicated that they have assumed the supplemental restriction requirement to be an election of species since according to Applicants the Office Action states that the required election is for purposes of examination and not prosecution.

It is noted that the supplemental restriction requirement in Paper No. 9 was not an election of species. In fact, the Office Action never indicated that such requirement was an election of species and clearly indicated that each of the multiple polynucleotides/polypeptides recited in the claims was an independent and patentably distinct invention. Furthermore, there was never any reference in Paper No. 9 of the supplemental restriction requirement to be just for purposes of examination and not prosecution. Applicants are reminded that the criteria for restriction for patentably distinct inventions according to MPEP 803 is that the inventions must be independent or distinct and there must be a serious burden on the Examiner. The Examiner clearly indicated the reasons why the claimed polynucleotides/polypeptides are independent and patentably distinct inventions and why the search of all of them would impose an undue burden on the Examiner (pages 4 and 5). It is also noted that on page 4, first paragraph of "Supplemental Restriction Requirement", the Examiner clearly indicated that the restriction was being applied under 37 CFR 1.142, which refers to restriction and not under 37 CFR 1.146, which refers to election of species.

In regard to arguments that the polynucleotides/polypeptides of the instant applications are part of a Markush group and so closely related that they should be examined together, as indicated above, each one of the polynucleotides is considered an independent and patentably distinct invention for the reasons indicated in previous Office Action Paper No. 9. As such, they are not considered part of a Markush group. It is noted that the MPEP 803.4 clearly states that nucleotides which encodes different polypeptides are a structurally distinct chemical compounds and unrelated to one another. While the Examiner acknowledges Applicant's assertion that the DNA molecules being claimed are related structurally and functionally, a complete search of all

the polynucleotides claimed (i.e. the polynucleotides of SEQ ID NO: 8, 20, 22, 24, 26, 36, 38, 40, 42 and the polynucleotides encoding the polypeptides of SEQ ID NO: 21, 23, 25, 27, 37, 39, 41 and 43) will still require a sequence search of each of the polynucleotides claimed, patented and non-patented literature searches, as well as a class/subclass search. These searches as indicated previously may not be co-extensive either.

The requirement is deemed proper and therefore is made FINAL.

It is noted that claims 43-45 and 54-58 are drawn to the non-elected polynucleotide of SEQ ID NO: 8. Claims 26-33, 38-40, 43-61 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

It is noted that some of the elected claims are still partially drawn to non-elected inventions. Examination of such claims will be restricted to the subject matter elected, which in the instant case is the polynucleotide of SEQ ID NO: 20, host cells comprising and expression of said polynucleotide. Applicants are requested to amend the claims accordingly in response to this Office Action.

Specification

1. The specification is objected for not complying with sequence rules. Applicant is required to insert sequence identifiers in front of sequences referred to in the specification and/or the drawings. See, for example, Figure 1 and references to such figure throughout the specification (37 CFR 1.821(d)). Appropriate correction is required.

Priority

2. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 120 or 121 to US application No. 09/598,982 filed on 6/21/2000.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 3/22/2001 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Drawings

4. The drawings have been reviewed and are objected under 37 CFR 1.84 or 1.152. See attached Notice of Draftsperson's Patent Drawing Review. Applicant is required to submit the drawing corrections within the time period set in the attached Office communication. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in ABANDOMENT of the application. In addition, if amendments to the specification are needed due to drawing corrections, Applicant is requested to submit such amendments while the case is being prosecuted to expedite the processing of the application.

Claim Objections

5. Claims 7-8 and 17-18 are objected to because they are partially drawn to non-elected inventions. Examination of such claims will be restricted to the subject matter elected, which in

the instant case is the polynucleotide of SEQ ID NO: 20. Appropriate correction is required..

Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-12, 41 and 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claims 1 and 41 (claims 2-12 and 42 dependent thereon) are indefinite in the recitation of "hosts transformed to contain the expression construct" for the following reasons. It is unclear what the meaning of the term "hosts" is within the context of the claims. As known in the art, transformation with recombinant DNA can be performed on single cells or in multicellular organisms (transgenic animals and plants), therefore the term "hosts" can be interpreted as either single cells or multicellular organisms. Also, it is noted that the term "hosts" has not been defined in the specification either. If the intended meaning is "host cells", that term would also be considered indefinite since it is unclear how one can obtain an active proteolytic tryptase if the construct is expressed in prokaryotic cells. It is suggested that if the term's intended meaning is "eukaryotic host cell", the claims be amended accordingly. For examination purposes, it will be assumed that the intended meaning of the term is "eukaryotic host cell". Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-6, 9-16, 19-25, 34-37, 41-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 9-13, 19 are drawn to a genus of DNA constructs comprising a genus of polynucleotides encoding inactive proteolytic tryptases from any organism wherein the inactivation is due to any active site mutation. Claims 2-3, 14 and 15 add the limitation that the tryptases are either β-1 or β-2 tryptases whereas claims 4 and 16 add the limitation that the tryptases are of human origin. Claims 5-6 are also drawn to the construct of claim 1 with the added limitation that the active site mutation changes the native amino acid to a non-charged amino acid or to an alanine residue. Claims 20-25 are drawn to a method of producing the inactive proteolytic tryptase of claim 1 whereas claims 34-37 are drawn to an eukaryotic host cell comprising the DNA construct of claim 1. Claim 41 is drawn to a genus of DNA constructs comprising a genus of polynucleotides encoding active proteolytic tryptases from any organism. Claim 42 adds the limitation that the tryptases are of human origin. The specification discloses one human β-1 and one human β-2 tryptase. The specification also discloses that the active sites of the tryptases disclosed in the specification (page 11, last paragraph) correspond to positions 44, 91 and 194 of the mature tryptase (no signal peptide). Furthermore, the specification teaches

the construction of several mutated forms of the human β-2 tryptase in Table 1, page 35 wherein the amino acids corresponding to positions 44, 91 and 194 have been changed to alanine residues. However, there is no disclosure of other human β-1 or β-2 tryptases or tryptases from other organisms as encompassed by the claims, nor there is disclosure of the corresponding active site amino acids which would inactivate the tryptases.

While one could argue that the genus of DNA constructs of the instant claims are adequately described since one can isolate polynucleotides encoding tryptases by sequence comparison using the polypeptide/polynucleotide structures disclosed in the instant application or the prior art, the state of the art teaches that sequence comparison alone should not be used to determine a protein's function and that small amino acid changes can drastically change the function of a polypeptide. Bork (Genome Research, 10:398-400, 2000) teaches protein function is context dependent, and both molecular and cellular aspects must be considered (page 398). Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995) teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* where found to be hydroxylases once tested for activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. (Science 282:1315-1317, 1998) teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. The specification only discloses a few species which is insufficient to put one of ordinary skill in the art in possession of (1) all attributes and features of all species within the genus and (2) all attributes and features of all species within the genus of

DNA constructs to practice the claimed method. Thus, one skilled in the art cannot reasonably conclude that Applicant had possession of the claimed invention at the time the instant application was filed.

11. Claims1-6, 9-16, 19-25, 34-37, 41-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the DNA construct comprising the polynucleotide of SEQ ID NO: 20 or the polynucleotide encoding the polypeptide of SEQ ID NO: 21, does not reasonably provide enablement for a DNA construct comprising any polynucleotide encoding (1) any inactive or active tryptase from any organism, (2) any inactive or active human tryptase, (3) any inactive β-I tryptase or (4) any inactive β-II tryptase, nor does it reasonably provide enablement for a method of using such DNA construct. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The criteria for undue experimentation, summarized in *re Wands*, 8, USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims.

The scope of the claims is not commensurate with the enablement provided in regard to the extremely large number of polynucleotides encoding tryptases encompassed by the claims. As indicated above, while the specification discloses one human β-I and one human β- II tryptase which have been modified at specific positions so that they are no longer enzymatically

active, there is no description of other tryptases from humans or other organisms, nor there is disclosure of which are the active sites of such tryptases which can be mutated to obtain enzymatically inactive tryptases. The state of the art teaches the unpredictability of the art in regard to the isolation of polynucleotides/polypeptides having the desired function based on sequence homology. See the teachings of Bork (Genome Research, 10:398-400, 2000), Broun et al. (Science 282:1315-1317, 1998), Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995) and Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) already discussed. Since the amino acid structure of a polypeptide determines its function, one of skill in the art would require some knowledge or guidance as to how structure relates to function in order to isolate polynucleotides encoding polypeptides of tryptase activity and determining their corresponding active sites in order to inactivate them. Therefore, due to the lack of relevant examples, the amount of information provided, the lack of knowledge about the critical structural elements required to maintain the desired function, and the unpredictability of the prior art in regard to function based on homology, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to screen and isolate those polynucleotides encoding tryptases as encompassed by the claims. Similarly, one of skill in the art would have to go through the burden of undue experimentation to practice the claimed method with such polynucleotides. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 41-42 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 6274366. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 1-7 of U.S. Patent No. 6274366 are drawn to a DNA construct comprising a promoter, a signal sequence and a polynucleotide encoding a human β-tryptase, wherein the construct drives the expression of enzymatically active human β-tryptase. Claims 41-42 of the instant application are drawn to a DNA construct comprising a promoter, a signal sequence and a polynucleotide encoding any proteolytic tryptase, wherein the construct drives the expression of an enzymatically active mature proteolytic tryptase. Since the

tryptase of U.S. Patent No. 6274366 is a mature polypeptide, claims 1-7 of U.S. Patent No. 6274366 anticipate the instant claims as written.

Allowable Subject Matter

14. Claims 17-18 are allowable over the prior art of record but are objected to since they depend upon a rejected base claim.

Conclusion

15. No claim is in condition for allowance.

16. Applicants are requested to submit a clean copy of the pending claims (including amendments, if any) in future written communications to aid in the examination of this application.

17. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
February 10, 2003

REBECCA E. PROUTY
PRIMARY EXAMINER
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